

*Lewis Acid Catalysis of Carbon-Carbon Bond Forming Reactions in Water*¹

2.1 Abstract

The use of water as a medium for performing organic reactions has so far only seen a limited number of applications despite the fact that the majority of biochemical processes takes place in this solvent. Recently the use of water as a solvent for organic synthesis has become increasingly popular.² Lewis acid catalysts in water has received even less attention over the past decades and only in the past few years the potential of Lewis acid catalysis in water has been recognized. In this chapter Lewis acid catalysis of carbon-carbon bond forming reactions in water is reviewed.

2.2 Introduction

Water is by far the most common liquid in our environment. Although rare elsewhere in the universe, the proportion of water in our bodies is close to that of water in a thin surface layer of the earth ~ 70%. Water is made up of H₂O molecules, though for a good part of the nineteenth century people thought the formula was OH. The H₂O molecules are bent, with a HOH angle of 104.5°. If the molecules of water were not bent, theorists predict that it would be a gas at room temperature. Life would not be the same....

Most synthetic reactions are performed in organic solvents. The use of water as the reaction medium is usually avoided since various reactants decompose when brought into contact with water. Furthermore, many organic reactants are sparsely soluble in water. Despite these disadvantages, water is becoming increasingly popular as a medium for organic reactions. Being the most abundant solvent on earth, it is very cheap, it is non-hazardous to the environment and non-toxic. Moreover, aqueous solvents can have beneficial effects on rates and selectivities of important organic transformations such as, for example, Diels-Alder reactions, aldol condensations and Michael additions.³ Finally, the use of water often simplifies work-up procedures. These features, in combination with the ever more strict legislation concerning industrial chemical processes, has led to increased efforts to transfer reactions from organic to aqueous solvents.⁴ On an industrial scale, the first example of this development is the Ruhr Chemie Rhone-Poulenc hydroformylation process.⁵

¹ This overview was modified from a previously published manuscript: Engberts, J.B.F.N., Feringa, B.L., Keller, E., Otto, S. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 457.

² Grieco, P.A. Ed. *Organic Synthesis in Water* Thomson Science, Glasgow, **1998**; Li., C., Chan, T.-H. *Organic reactions in Aqueous Media*, Wiley, New York, **1997**.

³ For review see: Lubineau, A., Augé, J., Queneau, Y. *Synthesis* **1994**, 741.

⁴ Recent reviews: Kalck, P., Monteil, F. *Adv. Organometal. Chem.* **1992**, *34*, 219; Herrmann, W.A., Kohlpainter, C.W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524; Haggins, J., *Chem. Eng. News* **1994**, *28*; Roundhill, D.M. *Adv. Organometal. Chem.* **1995**, *38*, 155.

⁵ Kuntz, E.G. *Chemtech* **1987**, 570.

Recently, Lewis acid catalyzed carbon-carbon bond forming reactions have been of growing interest in organic synthesis because of their unique reactivities, selectivities and mild reaction conditions used.⁶ While various kinds of Lewis acid promoted reactions have been developed and many have been applied in industry, these reactions must be carried under strict anhydrous conditions. The presence of even a trace of water ruins the reaction, because most Lewis acids react with water rather than with the substrates and are deactivated or totally decomposed in the presence of water. This fact has restricted the use of Lewis acids drastically.

Also in the field of Lewis-acid catalysis water is becoming increasingly popular, even though this solvent imposes severe restrictions on the applicability of Lewis acids. Active Lewis acids like BF_3 , TiCl_4 and AlCl_3 react violently with water and cannot be used. Moreover, coordination of the Lewis acid to the reactants is not as efficient in water as in solvents like methylene chloride or benzene. Hence, applications of Lewis-acid catalysis in water are still limited. An extensive review of Lewis-acid catalysis in water was published by Hay in 1987.⁷ Most of the efforts in this field are concerned with hydrolysis reactions of coordinated reactants. In 1993, Li reviewed carbon-carbon bond forming reactions in water.⁸ In neither review much attention was paid to aqueous carbon-carbon bond forming reactions catalyzed by Lewis acids. This is a rapidly developing, though relatively new field in organic chemistry and Kobayashi has already reviewed his pioneering work on this subject.⁹ A more recent overview of the progress made in this field will be provided here.

2.3 Lewis-acid Lewis-base interactions in water

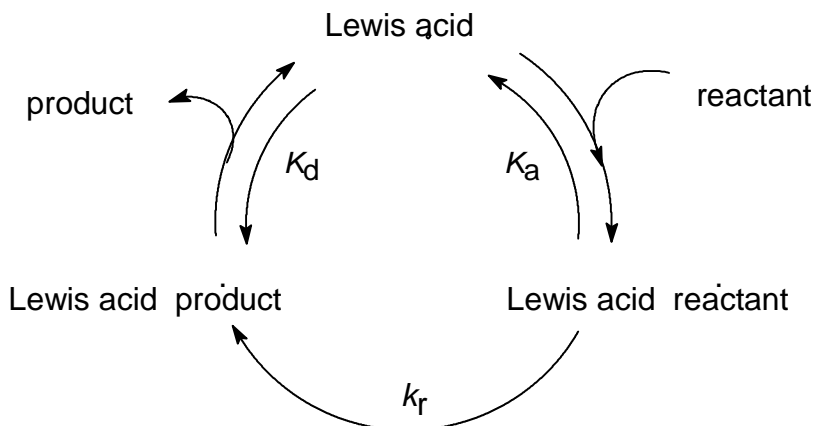
The first step in Lewis-acid catalysis is coordination of the Lewis-acid to a Lewis-basic site of a reactant. Most often this Lewis-basic site consists of one or more oxygen or nitrogen atoms. Coordination of the Lewis acid induces a polarization of part of the reactant molecule in conjugation with, or in the proximity of, this site by withdrawing electron density from the reactant to the catalyst. This activates the molecule with respect to the second step, the actual organic transformation. In the final step, the Lewis-acid product complex dissociates, making the catalyst available for another cycle. The overall catalytic efficiency is determined by the ease with which each of these steps proceeds, as quantified by K_a , k_r and K_d (Scheme 1.10).

⁶ Santelli, M., Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*, CRC Press, Boca Raton, Florida, **1996**.

⁷ Hay, R.W. in *Comprehensive Coordination Chemistry*, Chapter 61.4, G. Wilkinson, R.D. Gillard and J.A. McCleverty, eds., Pergamon Press, Oxford, **1987**.

⁸ Li, C. *Chem. Rev.* **1993**, 93, 2023.

⁹ Kobayashi, S. *Synlett* **1994**, 689.



Scheme 2.1

For most Lewis acid catalyzed processes the rate constant of the second step, k_r , is not high. Values of k_r for bimolecular reactions are typically in the order of $0.01 - 10 \text{ M}^{-1}\text{s}^{-1}$. In order to obtain an appreciable overall rate, a significant portion of reactant molecules has to be coordinated to the Lewis acid. Moreover, there is a qualitative, and sometimes even quantitative,¹⁰ correlation between K_a and k_r , which implies that when the Lewis acid coordinates the reactant efficiently, it will usually also lead to efficient polarization. In general, efficient coordination will ensure efficient catalysis but only as long as there is no catalyst poisoning by the product, *i.e.*, the equilibrium constant for coordination of the product to the catalyst, K_d , should not be too high.

The most frequently used solvents for Lewis-acid-catalyzed reactions are aprotic, apolar solvents like methylene chloride or benzene. Polar and protic solvents are usually avoided. This is due to solubility problems encountered when using relatively apolar reagents, incompatibility of the catalyst with these solvents and the inefficient coordination of the reactant to the Lewis acid in these solvents. These effects are particularly pronounced in water.

In order to understand the way in which solvents in general, and water in particular, affect the interactions between a Lewis acid and a Lewis base, a thorough understanding of these interactions is required. An important approach involves the Hard-Soft-Acid-Base (HSAB) theory, as developed by *Pearson* in 1963.¹¹ According to this theory, Lewis acids and Lewis bases are divided into two groups: hard acids and bases, which are usually small, not very polarizable species with highly localized charges, on one hand, and soft acids and bases which are large polarizable species with delocalised charges on the other hand. A selection of Lewis acids, ordered according to their hardness in aqueous solution is presented in Table 1. The theory predicts high stabilities for hard-acid hard-base complexes, mainly resulting from electrostatic interactions and for soft-acid soft-base complexes, where covalent bonding is also important. Hard-acid soft-base and hard base-soft acid complexes have

¹⁰ Nakon, R., Rechani, P.R., Angelici, R.J. *J. Am. Chem. Soc.* **1974**, 96, 2117.

¹¹ Pearson, R.G. *J. Am. Chem. Soc.* **1963**, 85, 3533; Pearson, R.G. *J. Chem. Educ.* **1987**, 64, 561; Pearson, R.G. *Coord. Chem. Rev.* **1990**, 100, 403.

usually small stabilities. Unfortunately, in a quantitative sense, the predictive value of the HSAB theory is limited.

Table 1 Classification of some selected Lewis acids according to the HSAB theory in aqueous solution^a.

Hard	Borderline	Soft
H ⁺	Fe ²⁺	Cu ⁺
Mn ²⁺	Co ²⁺	Ag ⁺
Fe ³⁺	Ni ²⁺	Hg ²⁺
Co ³⁺	Cu ²⁺	Cd ²⁺
Al ³⁺	Zn ²⁺	
La ³⁺		

^a Taken from Ref. 11a.

Table 2 Donor scales of some selected solvents.

Solvent	D_S^a	DN^b	DN_{bulk}^c
Methylene chloride	6		
Benzene	9	0.1	0.8
Acetonitrile	12	14.1	11.1
Water	17	18.0	40.3
Methanol	18	19	31.3
Dimethylsulfoxide	27.5	29.8	27

^a Donor strengths, taken from Ref. 15, based upon the solvent effect on the symmetric stretching frequency of the soft Lewis acid HgBr₂. ^b Gutmann's donor number taken from Ref. 15, based upon ΔH_f for the process of coordination of an isolated solvent molecule to the moderately hard SbCl₅ molecule in dichloroethane. ^c Bulk donor number calculated as described in Ref. 12 from the solvent effect on the adsorption spectrum of VO(acac)₂. Several other attempts have been made to define a Lewis-acidity scale.¹³

In view of the HSAB theory, the applicability of a scale which describes Lewis acidity with only one parameter will be unavoidably restricted to a narrow range of structurally related Lewis bases. The use of more than one parameter results in relationships with a more general validity.¹⁴ However, a quantitative prediction of the gas-phase stabilities of Lewis-acid Lewis-base complexes is still difficult. Hence the interpretation, not to mention the prediction, of solvent effects on Lewis-acid Lewis-base interactions remains largely speculative. Consequently, the effects that are considered to be important in rationalizing the

¹² Marcus, Y. *J. Solution Chem.* **1984**, 13, 599.

¹³ See for example Laszlo, P., Teston, M. *J. Am. Chem. Soc.* **1990**, 112, 8750; Luo, Y., Benson, S.W. *Inorg. Chem.* **1991**, 30, 1676 and references cited therein.

¹⁴ Drago, R.S., Wayland, B.B. *J. Am. Chem. Soc.* **1965**, 87, 3571; Drago, R.S. *Structure and Bonding* **1973**, 15, 73; Drago, R.S. *J. Chem. Educ.* **1974**, 51, 300; Drago, R.S., Parr, L.B., Chamberlain, C.S. *J. Am. Chem. Soc.* **1977**, 99, 3203.

influence of the solvent on Lewis-acid Lewis-base equilibria, can only be treated in a qualitative manner.

First of all, the solvent will, in most cases, also act as a Lewis base by coordinating to the catalyst. Analogous to the Lewis-acidity scales, solvents have been ranked according to their Lewis basicity. These scales, in as far as they try to quantify Lewis basicity using only one parameter, also have limited validity. An extensive discussion of the electron pair donor ability and Lewis basicity scales of solvents is given in Ref. 15. In Table 2 a number of Lewis acidity parameters of some relevant solvents are compared. It is apparent that aprotic and apolar solvents coordinate relatively weakly to the catalyst, whereas polar solvents exhibit stronger interactions. In the latter solvents coordination of a Lewis base is less favorable as a result of the strong solvent Lewis-acid interaction which has to be disrupted. Steric interactions between the Lewis base and coordinated solvent molecules are also important in determining the stability of the complex¹⁶. Consequently, catalysis by Lewis acids in solvents that coordinate strongly to the Lewis acid will be less effective.

Table 3 Acceptor numbers (*AN*) and hydrogen bond donor acidities (α) of some selected solvents.

Solvent	<i>AN</i> ^a	α ^b
Methylene chloride	20.4	0.00
Benzene	8.2	(0.30)
Acetonitrile	19.3	0.19
Water	54.8	1.17
Methanol	41.3	0.93
Dimethyl sulfoxide	19.3	0.00

^a Taken from Ref. 17, based on the ³¹P-NMR chemical shift of triethylphosphine oxide in the respective pure solvent. ^b Taken from Ref. 15b based on the solvatochromic shift of a pyridinium-*N*-phenoxide betaine dye.

The second important influence of the solvent on Lewis-acid Lewis-base equilibria is its interaction with the Lewis base. Consequently, the Lewis acidity and, when hard Lewis bases are concerned, the hydrogen bond donor capacity of the solvent, are important parameters. The electron pair acceptor capacities, quantified by the acceptor number *AN*, together with the hydrogen bond donor acidities, α , of some selected solvents are listed in Table 3. Water is among the solvents with the highest *AN* and, accordingly, will interact strongly with Lewis bases. This seriously hampers the efficiency of Lewis-acid catalysis in water.

¹⁵ Sandström, M., Persson, I., Persson, P. *Acta Chem. Scand.* **1990**, *44*, 653; Reichardt, C. in *Solvents and Solvent Effects in Organic Chemistry*, VCH, Weinheim, **1988**.

¹⁶ Hancock, R.D., Martell, A.E. *Adv. Inorg. Chem.* **1995**, *42*, 89.

¹⁷ Mayer, U., Gutmann, V., Gerger, W. *Monatshefte Chem.* **106**, 1235 (1975). (b) Gutmann, V. in *The Donor Acceptor Approach to Molecular Interactions*, Plenum Press, New York, **1978**.

Thirdly, the intramolecular association of a solvent affects the Lewis-acid Lewis-base equilibrium.¹⁸ Upon complexation, one or more solvent molecules that were initially coordinated to the Lewis acid or the Lewis base, are liberated into the bulk liquid phase, a process which is entropically favorable. This effect is more pronounced in aprotic solvents than in protic solvents, which usually have a higher cohesive energy density. The less favorable entropy change in protic solvents is somewhat counteracted by the more favorable enthalpy change upon release of a coordinated solvent molecule into the bulk liquid, resulting from the newly formed hydrogen bonds.

Finally, the solvent also interacts with sites of the Lewis acid and the Lewis base that are not directly involved in mutual coordination, thereby altering the electronic properties of the complex. For example, delocalization of charges into the surrounding solvent molecules causes ions in solution to be softer than in the gas phase.¹⁶ Again, water is particularly effective since it can act as an efficient electron-pair acceptor as well as donor.

In summary, we conclude that complexation of a Lewis acid to a Lewis base is seriously hampered by water.¹⁹ Since water interacts through either oxygen or hydrogen atoms, it can be classified as a hard solvent (Table 4). This implies that it will interfere most strongly with the interactions between hard Lewis acids and hard Lewis bases. Soft soft interactions, on the other hand, will be much less affected.^{11b} However, this is of limited practical use in Lewis acid catalysis, since the majority of reactants contain electronegative and hard elements as Lewis-basic sites.

Table 4. Softness of some selected solvents according to the μ -scale.

Solvent	μ^a
Acetonitrile	0.35
Water	0.00 ^b
Methanol	0.02
Dimethyl sulfoxide	0.22

^a Taken from Ref. 20, resulting from a comparison of $\Delta G_{tr}^0(\text{water} \rightarrow \text{solvent})$ for Ag^+ with the mean of $\Delta G_{tr}^0(\text{water} \rightarrow \text{solvent})$ for Na^+ and K^+ . ^b By definition.

Thermodynamic analysis clearly shows a difference in the way water affects hard-hard interactions, compared to soft-soft interactions. In water, hard-hard interactions are usually endothermic and occur only as a result of a gain in entropy, originating from a liberation of water molecules from the hydration shells of the Lewis acid and the ligand. By contrast, soft-soft interactions are mainly enthalpic in origin and are characterized by a negative change in entropy.²¹

¹⁸ Persson, I. *Pure Appl. Chem.* **1986**, 58, 1153.

¹⁹ Åhrland, S. *Pure Appl. Chem.* **1979**, 51, 2019.

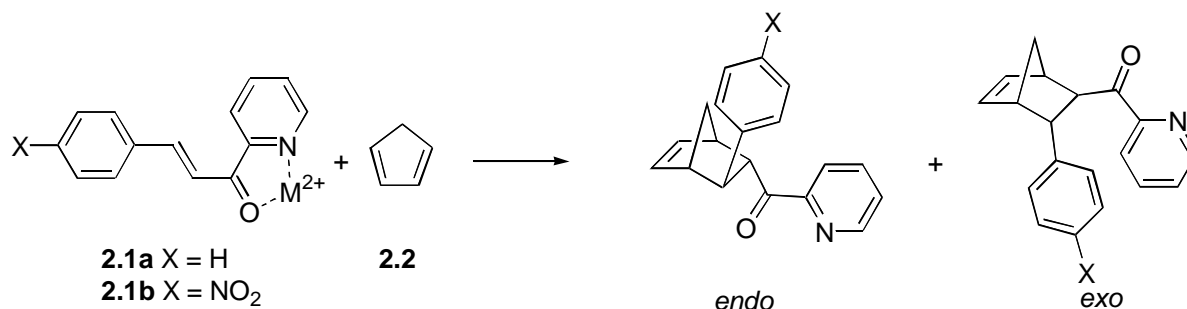
²⁰ Marcus, Y. *J. Phys. Chem.* **1987**, 91, 4422.

²¹ Åhrland, S. *Helv. Chim. Acta* **1967**, 50, 306; Åhrland, S. *Structure and Bonding* **1973**, 15, 167.

2.4 Lewis Acid catalyzed reactions in water

2.4.1 The Diels-Alder reaction

The rate of the Diels-Alder reaction was traditionally considered to be insensitive to the solvent. However, in 1980, Breslow showed that this reaction can be accelerated considerably when performed in water²². The *endo-exo* selectivity also benefits from the use of this solvent. The preference for the *endo* cycloadduct usually observed, becomes more pronounced in water. A large number of papers have appeared discussing the origin of these remarkable observations.^{23,24} Evidence has been presented that there are two effects causing this aqueous rate and selectivity enhancement: enforced hydrophobic interactions and hydrogen bonding to the activating group of the dienophile.



Scheme 2.2 Lewis acid catalyzed Diels-Alder reaction in water.

Lewis acids are also known to increase the rate and selectivity of Diels-Alder reactions.²⁵ The combination of Lewis acid catalysis and water was not, however, studied until 1995, when it was shown that the Diels-Alder reaction between 3-(4-nitrophenyl)-1-(pyrid-2-yl)-2-propen-1-one (**2.1a**) and cyclopentadiene (**2.2**) was subject to Lewis acid catalysis in water (Scheme 2.2).^{26,27,28} The rate of this reaction has been determined in several solvents. It is clear that very large accelerations can be achieved by the combined use of a Lewis acid as a catalyst and water as the solvent. However, the large rate enhancement in going from acetonitrile to water for the uncatalyzed reaction is strongly reduced in the case of the copper (II) catalyzed reaction. The selectivity of the catalyzed reaction is slightly decreased in water. The catalytic efficiency of the reaction is determined by the equilibrium constant (K_a) for binding of the dienophile to the catalyst and by the rate constant (k_r) of the subsequent reaction with **2.2** (Scheme 2.2). The bidentate character of the dienophile **2.1** is essential in order to obtain efficient catalysis. For the reaction 3-(4-nitrophenyl)-1-(pyrid-4-

²² Rideout, D.C, Breslow, R. *J. Am. Chem. Soc.* **1980**, 102, 7871.

²³ Eggelte, T.A., de Koning, H., Huisman, H.O. *Tetrahedron* **1973**, 29, 2491.

²⁴ See: Blokzijl, W., Blandamer, M.J., Engberts, J.B.F.N. *J. Am. Chem. Soc.* **1991**, 113, 4241; Otto, S., Blokzijl, W., Engberts, J.B.F.N. *J. Org. Chem.* **1994**, 59, 5372; Engberts, J.B.F.N. *Pure Appl. Chem.* **1995**, 67, 823; Wijnen, J.W., Zavarise, S., Engberts, J.B.F.N. *J. Org. Chem.* **1996**, 61, 2001.

²⁵ Pindur, U., Lutz, G., Otto, C. *Chem. Rev.* **1993**, 93, 741.

²⁶ Otto, S., Engberts, J.B.F.N. *Tetrahedron Lett.* **1995**, 36, 2645.

²⁷ Otto, S. *Catalysis of Diels-Alder Reactions in Water*, Ph.D. Thesis, University of Groningen, The Netherlands, **1998**.

yl)-2-propen-1-one **2.3** with cyclopentadiene, no catalysis is observed, because **2.3** is not capable of forming a chelate with the Lewis acid (Figure 2.1).

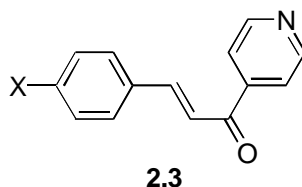
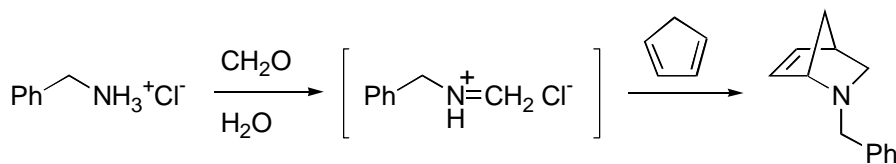


Figure 2.1

Recently Otto succeeded in performing copper (II) catalyzed enantioselective Diels-Alder reactions *in pure water* with e.e.'s up to 74 % using simple commercially available amino acids as the chiral ligand. This is the first example of an enantioselective Lewis acid catalyzed carbon-carbon bond forming reaction in water.²⁸

Recently Wang and co-workers²⁹ claimed catalysis of a hetero Diels-Alder reaction involving a monodentate *in-situ* generated dienophile. In 1985, Grieco had already reported that the Diels-Alder reaction between dienes and simple inactivated iminium salts, generated *in-situ* from formaldehyde and amine hydrochlorides under Mannich-like conditions, proceeds smoothly without catalyst (Scheme 2.3).³⁰ The scope of this reaction could be extended to the synthesis of optically pure heterocycles by employing chiral amines and amino acids³¹. Unfortunately, the synthetic applications of the uncatalyzed reaction are limited to either formaldehyde or activated aldehydes, higher aldehydes, such as 1-hexanone, showing much lower reactivity. However, the work of Wang shows that, by using lanthanide trifluoromethanesulphonates (triflates) as Lewis acid catalysts, the yield of the aza Diels-Alder adducts of higher aldehydes and cyclopentadiene can be increased considerably (Scheme 2.4). Moreover, the yield of the cycloadducts of the aza Diels-Alder reaction between phenylalanine methyl ester, formaldehyde and several dienes could be increased considerably when Nd(OTf)₃ was used as Lewis acid. However, the reaction of higher aldehydes with dienes other than cyclopentadiene was not successful either in the absence or in the presence of the lanthanide triflates. The authors did not suggest a mechanism by which the Lewis acid affects the two-step process.



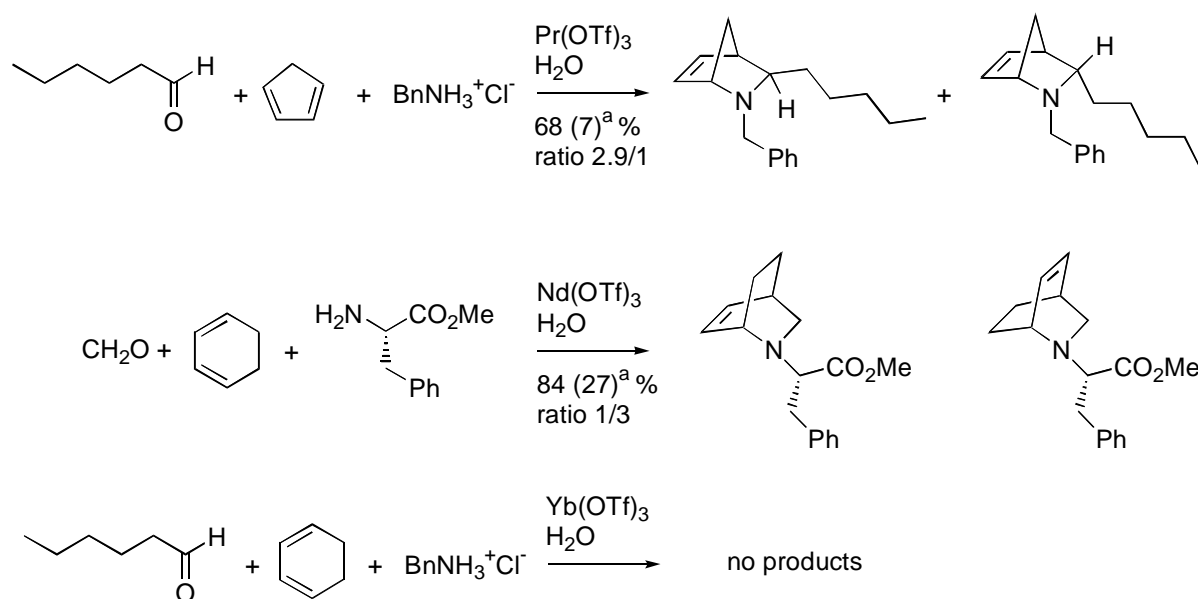
Scheme 2.3 Hetero-Diels-Alder reaction in water.

²⁸ Otto, S., Boccaletti, G., Engberts, J.B.F.N. *J. Am. Chem. Soc.* **1998**, *120*, 4238.

²⁹ Yu, L., Chen, D., Wang, P.G. *Tetrahedron Lett.* **1996**, *37*, 2169.

³⁰ Larsen, S.D., Grieco, P.A. *J. Am. Chem. Soc.* **1985**, *107*, 1768; Grieco, P.A., Larsen, S.D. *Org. Synth.* **1990**, *68*, 206.

³¹ Grieco P.A., Bahsas, A. *J. Org. Chem.* **1987**, *52*, 5746; Waldman, H. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 274; Waldman, H., Braun, M. *Liebigs Ann. Chem* **1991**, 1045.



Scheme 2.4 Lewis acid catalyzed Hetero-Diels Alder reaction.

^a Yield without catalyst

2.4.2 The aldol reaction

The Lewis-acid-catalyzed aldol reaction of silyl enol ethers, commonly known as the Mukaiyama aldol reaction, was first reported in the early seventies. This titanium-tetrachloride-catalyzed cross-aldol reaction³² proceeds in a regioselective manner, giving high yields. These transformations are normally carried out under strictly non-aqueous conditions to prevent decomposition of the catalyst and hydrolysis of the silyl enol ethers used in the reaction.

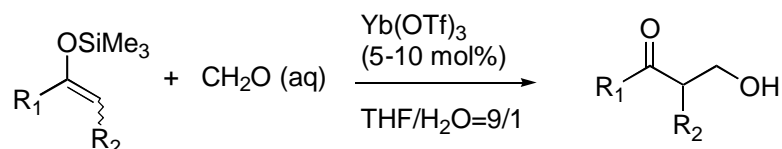
Kobayashi³³ reported the first Lewis-acid-catalyzed cross-aldol reaction in aqueous solution. He examined the effects of lanthanide triflates in the reaction of several silyl enol ethers with a commercial formaldehyde solution (Scheme 2.5). The same reaction in the absence of catalyst was previously studied by Lubineau,³⁴ who reported the water-promoted aldol reaction of silyl enol ethers with aldehydes. However, the scope and yields were not satisfactory. When the reaction was performed in the presence of a Lewis-acid catalyst, in most cases the silyl enol ethers reacted smoothly with formaldehyde to give the corresponding hydroxymethylated product in high yields. The reactions were most effectively carried out in a 1/9 commercial aqueous formaldehyde/THF mixture under the influence of 5-10 mol% of Yb(OTf)_3 . After completion of the reaction, nearly 100% of the Yb(OTf)_3 catalyst was recovered from the aqueous layer and could be re-used quite easily.³⁵

³² Mukaiyama, T., Narasaka, K., Banno, K. *Chem. Lett.* **1973**, 1011; Mukayama, T., Banno, K. Narasaka, K. *J. Am. Chem. Soc.* **1974**, 96, 7503.

³³ Kobayashi, S. *Chem. Lett.* **1991**, 2087.

³⁴ Lubineau A., Meyer, E. *Tetrahedron* **1988**, 44, 6065.

³⁵ Kobayashi, S., Hachiya, I., Yamanoi, Y. *Bull. Chem. Soc. Jpn.* **1994**, 67, 2342.



Scheme 2.5 Lewis acid catalyzed aldol reaction.

Various aldehydes could be used to obtain the cross-aldol product in high yield as a mixture of *syn* and *anti* isomers.³⁶ For example, water-soluble aldehydes, such as acetaldehyde, acrolein and chloroacetaldehyde react with silyl enol ethers to give the corresponding cross-aldols. Benzaldehyde, substituted benzaldehydes and higher aldehydes gave good results in this reaction. Even salicylaldehyde and 2-pyridinecarboxaldehyde have been employed successfully. This is remarkable because the free hydroxyl group, present in the former compound, and the pyridine nitrogen, present in the latter, can give problems due to undesired coordination to the Lewis acid in organic solvents. The amount of water in the reaction mixture is crucial. The best results were obtained when the organic solvent contained 10-20% (v/v) of water. When the amount of water increased, the yield of aldol product decreased. This drop in yield is caused by the competitive hydrolysis of the silyl enol ether, which precedes the desired aldol reaction.

2.4.3 Allylation reactions

The synthesis of homoallylic alcohols via a Lewis-acid-catalyzed reaction of alkylorganometallic reagents with a carbonyl compound has been widely studied.³⁷ The first example of such a Lewis-acid-catalyzed allylation reaction in aqueous medium was again reported by Kobayashi.³⁸ In a smooth reaction under the influence of 5 mol% of Sc(OTf)_3 , tetraallyltin was allowed to react with several ketones and aldehydes (Table 5). The reactions were carried out in water/THF, water/ethanol or water/acetonitrile mixtures (1/9) providing high yields of the corresponding homoallylic alcohol. Furthermore the reaction of unprotected sugars gave the desired product directly, again in high yield. Unprotected phenols such as salicylaldehyde can also be used in this reaction. Some typical examples are listed in Table 5. The much cheaper Yb(OTf)_3 is also effective and the Lewis acid can be re-used without loss of activity.³⁹

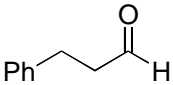
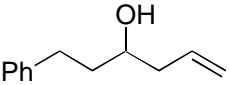
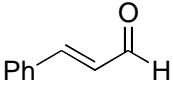
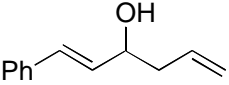
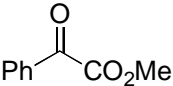
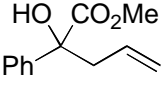
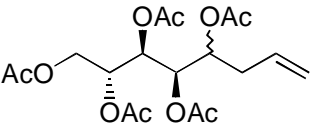
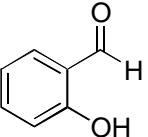
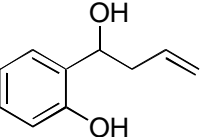
³⁶ Kobayashi, S., Hachiya, T. *Tetrahedron Lett.* **1992**, 33, 1625; Kobayashi, S., Hachiya, T. *J. Org. Chem.* **1994**, 59, 3590.

³⁷ For review see: Yamamoto, Y., Asao, N. *Chem. Rev.* **1993**, 93, 2207.

³⁸ Hachiya, I., Kobayashi, S. *J. Org. Chem.* **1993**, 58, 6958.

³⁹ Kobayashi, S., Hachiya, I., Yamanoi, Y. *Bull. Chem. Soc. Jpn.* **1994**, 67, 2342.

Table 5 Allylation of various aldehydes with tetraallyltin.³⁸

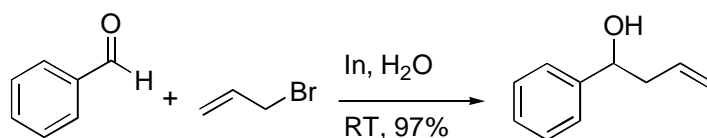
Carbonyl compound	Product	Solvent	Yield (%)
		THF/H ₂ O	92
		EtOH/H ₂ O	96
		MeCN/H ₂ O	96
		THF/H ₂ O	98
		THF/H ₂ O	87
D-arabinose		THF/H ₂ O	81 ^a
		THF/H ₂ O	100

^a isolated after acylation.

2.4.4 Barbier-type reactions

The use of indium in aqueous solution has been reported by Li and co-workers^{8,40} as a new tool in organometallic chemistry. Indium can be readily used to promote the allylation of aldehydes and ketones in water at room temperature without the need for an inert atmosphere (Scheme 2.6). In fact, protection of hydroxyl groups is not required and acid-sensitive groups such as an acetal functionality are left intact during allylation.

The use of a Lewis acid promotor can have a large effect on the stereoselectivity of the reaction.⁴¹ When Yb(OTf)₃ was used as a Lewis acid⁴² in the allylation of aldehyde **2.4** (Scheme 2.7), performed in water using DMF as a cosolvent, the diastereoselectivity was much higher than in the absence of Lewis acid (Table 6). Furthermore, the reaction time could be reduced to one hour. Compared to the reaction under aprotic conditions, using allylsilane instead of allylbromide/indium, almost complete reversal of diastereoselectivity was found.

**Scheme 2.6**

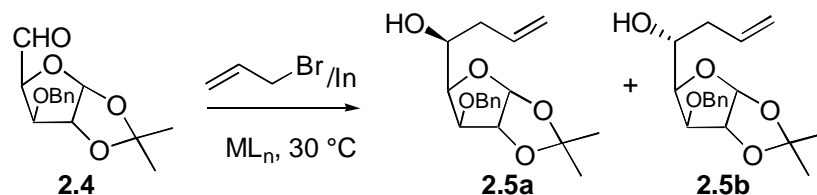
⁴⁰ Li, C.J. *Tetrahedron Lett.* **1991**, 32, 7017; Chan, T.H., Li, C.J., Lee, M.C., Wei, Z.Y. *Can. J. Chem* **1994**, 72, 1181; Cintas, P. *Synlett* **1995**, 1087.

⁴¹ Wang, R., Lim, G.-M., Tan, C.H., Lim, B.-K., Sim, K.-Y., Loh, T.-P. *Tetrahedron Asymmetry* **1995**, 6, 1825.

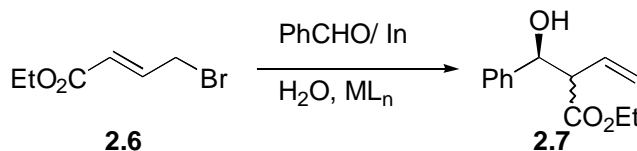
⁴² Stoichiometric amounts of Lewis acid were used in this reaction.

Table 6 Indium-promoted allylation.

ML _n	Solvent (time)	2.5a/2.5b (yield)
-	H ₂ O (10 h)	41/59 (66%)
-	DMF/H ₂ O = 4/1 (2 h)	17/83 (82%)
Yb(OTf) ₃	DMF/H ₂ O = 4/1 (1 h)	6/94 (88%)
AllylSiMe ₃ /SnCl ₄	CH ₂ Cl ₂ , -78 °C	88/12 (76%)

**Scheme 2.7** Indium-promoted allylation.

In the indium-mediated coupling reaction of ethyl (*E*)-4-bromoprop-2-enoate (**2.6**) with carbonyl compounds in water, providing β -hydroxy esters **2.7** (Scheme 2.8), the presence of La(OTf)₃⁴² also increases the rate and diastereoselectivity of the reaction,⁴³ as can be seen from the results in Table 7. The authors explain the high *anti* selectivity by assuming a cyclic transition state as is shown in Scheme 2.9. The role of the Lewis acid has not been further elucidated so far.

**Scheme 2.8**

More recently Loh showed that this concept could also be successfully employed in the stereoselective synthesis of β -trifluoromethylated homoallylic alcohols.⁴⁴ Furthermore the stereoselective synthesis of tertiary alcohols *via* indium mediated allylation of sugar derived ketones in pure water was accomplished.⁴⁵

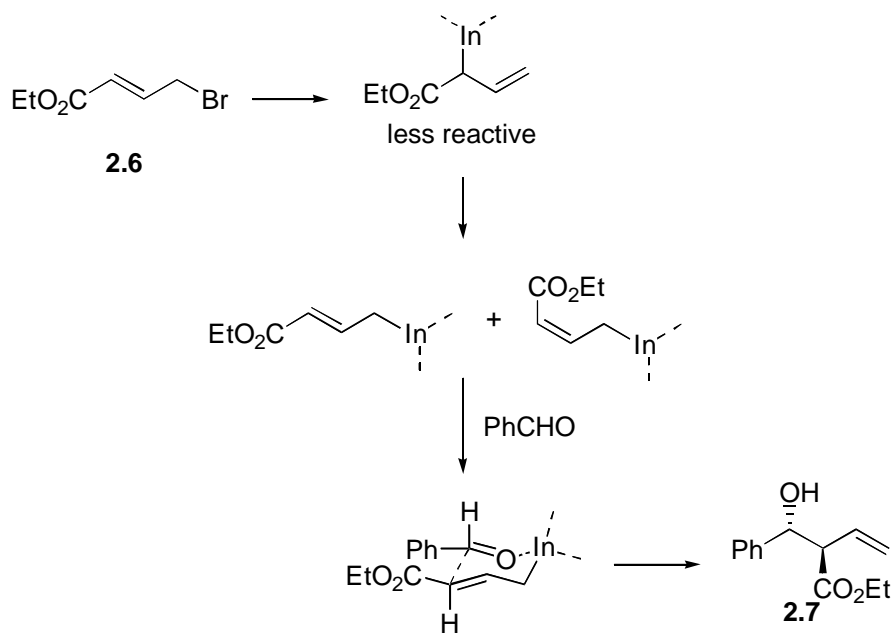
Table 7 Indium promoted allylation of benzaldehyde with γ -substituted allyl bromides

γ -substituent	ML _n	Solvent	yield %	Anti/syn
CO ₂ Et	-	H ₂ O	59	86/14
CO ₂ Et	La(OTf) ₃	H ₂ O	99	90/10
CO ₂ Et	La(OTf) ₃	DMF	92	86/14
Cis-CO ₂ Et	La(OTf) ₃	H ₂ O	90	99/1
Cis-CO ₂ Et	La(OTf) ₃	DMF	90	86/14

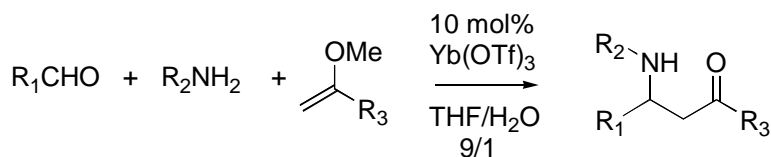
⁴³ Diana, S.-C.H., Sim, K.-Y., Loh, T.-P. *Synlett* **1996**, 263.

⁴⁴ Loh, T.-P., Li, X.-R. *Chem. Commun.* **1996**, 1929; Loh, T.-P., Li, X.-R. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 980.

⁴⁵ Loh, T.-P., Ho, D.S.-C., Chua, G.-L., Sim, K.-Y. *Synlett* **1997**, 563.



Scheme 2.9



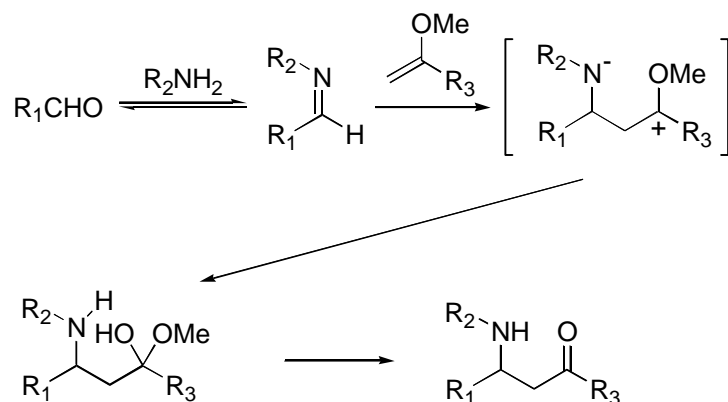
Scheme 2.10 Mannich-type reaction.

2.4.5 Mannich-type reaction

For the synthesis of β -amino ketones the Mannich reaction is one of the most attractive processes.⁴⁶ A new type of Lewis-acid-catalyzed Mannich reaction can be carried out conveniently in aqueous solution. An aldehyde, an amine and a vinyl ether are allowed to react in THF/water (9/1) mixtures, in the presence of 10 mol% of $\text{Yb}(\text{OTf})_3$, to give the β -amino ketone in 55-100% yield (Scheme 2.10).⁴⁷ Commercially available aqueous formaldehyde and chloroacetaldehyde solutions can be used directly. Phenyl oxoacetate monohydrate, methyl oxoacetate, aliphatic and α,β -unsaturated aldehydes also gave modest to high yields. The reaction is proposed to proceed via a mechanism involving imine formation and successive addition of a vinyl ether in aqueous solution (Scheme 2.11). Again, the catalyst could be recovered after the reaction was completed and re-used with comparable results.

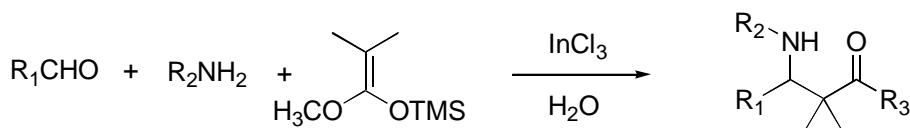
⁴⁶ House, H.O. in *Modern Synthetic Reactions* **1972**, 2nd Ed. Benjamin, W.A., Menlo Park, California, 654.

⁴⁷ Kobayashi, S., Ishitani, H.J. *J. Chem. Soc., Chem. Commun.* **1995**, 1379.



Scheme 2.11

More recently Loh described the one-pot Mannich type reaction of aldehydes, amines and silyl enol ethers in pure water for the synthesis of β -amino ketones and esters in moderate to good yields using InCl_3 as a reusable water stable Lewis acid (Scheme 2.12).⁴⁸ Furthermore, when glyoxylic acid monohydrate was used, α -amino acids were isolated in moderate yield.



Scheme 2.12

2.4.6 Micellar systems

Recently there has been some debate in the literature about the effect of some water stable Lewis acids in Mukaiyama type aldol reactions. Loh reported efficient catalysis of the reaction of silyl enol ethers with aldehydes in pure water without the use of cosolvent.⁴⁹ In contrast Kobayashi found that hydrolysis of the silyl enol ethers is superior to the desired condensation under the same conditions. However it was found that the reaction could be performed in water without the use of a cosolvent when small amounts of sodium dodecyl sulphate were added to the reaction mixture to obtain micellar systems.⁵⁰ Earlier Kobayashi already reported $\text{Sc}(\text{OTf})_3$ catalyzed aqueous aldol reactions of silyl enol ethers with aldehydes in the presence of surfactants without the use of organic solvent.⁵¹

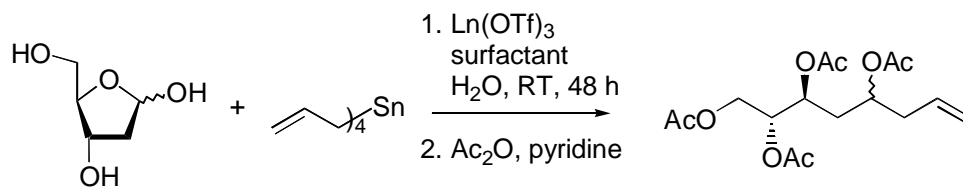
Although high yields and selectivities were obtained in the $\text{Sc}(\text{OTf})_3$ catalyzed allylation reactions of aldehydes, varying amounts of organic cosolvents were required for this reaction.³⁵ However when small amounts of surfactant were added to the reaction mixture the $\text{Sc}(\text{OTf})_3$ catalyzed allylation reactions of aldehydes proceeded smoothly in water even in the absence of

⁴⁸ Loh, T.-P., Wei, L.-L. *Tetrahedron Lett.* **1998**, 39, 323.

⁴⁹ Loh, T.-P., Pei, J., Cao, G.-Q. *J. Chem. Soc., Chem. Commun.* **1996**, 1819; Loh, T.-P., Pei, J., Koh, S.V., Cao, G.Q., Li, X.-R. *Tetrahedron Lett.* **1997**, 38, 3465; Loh, T.-P., Pei, J., Koh, S.V., Cao, G.Q., Li, X.-R. *Tetrahedron Lett.* **1997**, 38, 3993.

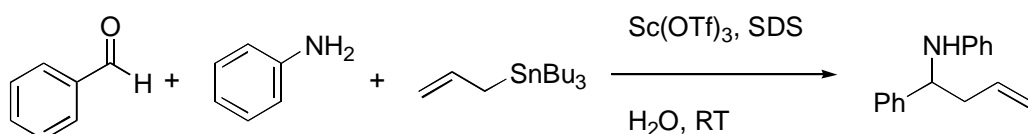
⁵⁰ Kobayashi, S., Busujima, T., Nagayama, S. *Tetrahedron Lett.* **1998**, 39, 1579.

organic solvent (Scheme 2.13).⁵² The reaction was sluggish without the Lewis acid or the surfactant.



Scheme 2.13

Sc(OTf)₃ also catalyzed the three component reactions of aldehydes, amines and allyltributyl stannane in micellar systems.⁵³ Without the use of organic solvents homoallylic alcohols could be obtained in high yields in the presence of a small amount of Sc(OTf)₃ and sodium dodecylsulphate (SDS), whereas the reaction was sluggish when one of these compounds was left out of the reaction mixture.



Scheme 2.14

In addition to the Yb(OTf)₃ catalyzed aldol and allylation reactions, Kobayashi recently reported their promising results using copper(II) triflates in water ethanol toluene mixtures for these reactions.⁵⁴

2.5 Conclusions and prospect

As a result of the growing need for clean chemistry, in particular by using catalytic processes and decreasing the use of organic solvents, Lewis acid catalysis in water will be a field of considerable interest in the future. Catalysis by soft Lewis acids in water is generally easier than catalysis by hard catalysts, as encountered in most carbon carbon bond forming reactions. In the slip stream of the success of the Ruhr Chemie Rhone Poulenc process, more breakthroughs in the former field can be expected in the coming years, whereas catalysis by hard Lewis acids in aqueous media will remain troublesome for the time being. Although so far many examples of Lewis acid catalyzed carbon-carbon bond forming reactions in aqueous media have been reported in many cases co-solvents were used. Reactions in pure water are of more interest for the future in order to (even) further exclude the use of organic solvent for chemical processes.

⁵¹ Kobayashi, S., Wakabayashi, T., Nagayama, S., Oyamada, H. *Tetrahedron Lett.* **1997**, 38, 4559.

⁵² Kobayashi, S., Wakabayashi, T., Oyamada, H. *Chem.Lett.* **1997**, 831.

⁵³ Kobayashi, S., Busujima, T., Nagayama, S. *Chem. Commun.* **1998**, 19.

⁵⁴ Kobayashi, S., Nagayama, S., Busujima, T. *Chem. Lett.* **1997**, 959.